

## Review

# A patient and physician friendly stimulation protocol using long acting FSH and progestin priming should be the future of IVF

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## Abstract

**Objective:** Needle phobias and concern about the discomfort remain significant disincentives for many women contemplating in vitro fertilization (IVF). The number of injections required in an IVF cycle is increased by the use of most medications which prevent premature ovulation. **Mechanism:** long-acting follicular stimulation hormone (LA-FSH) that was developed 15 years ago has the ability to stimulate folliculogenesis in a patient for seven days with a single injection, with comparable outcomes to daily injections in assisted reproduction. Many clinicians were hesitant to use it in their patients, fearing an inability to decrease levels of FSH stimulation for 7 days and the resultant increased risks of ovarian hyperstimulation syndrome (OHSS). This occurred prior to the widespread adoption of Gonadotropin-releasing hormone (GnRH)-agonist triggering and freeze all embryos for the prevention of OHSS. **Conclusions:** We suggest LA-FSH protocol with the use of progestins to prevent ovulation, which could be an alternative way to treat IVF patients without any compromise of the effectiveness of the treatments or the safety of the patients.

**Keywords:** injections; protocol; progestin

## 1. Introduction

Exogenous gonadotropins have been used to recruit follicles for in vitro fertilization (IVF) since the late 1980s, which results in multiple, self-administered, daily injections [1]. Gonadotropins are not orally active, and due to the short half-life, daily injections are needed to maintain the stimulation [2]. When first introduced, gonadotropins were obtained from menopausal urine and had to be given by intra muscular injection. As more purified urinary preparations and ultimately recombinant versions became available, it was determined that these injections could be given by the subcutaneous route and localized skin reactions became less common [3]. Despite these improvements, needle phobias and concern about the discomfort remain significant disincentives for many women contemplating IVF [3]. The number of injections required in an IVF cycle is increased by the use of most medications which prevent premature ovulation [4,5]. Although, intra-nasal injections of gonadotropin-releasing hormone (GnRH)-agonists can be used for this goal, they have not been widely adopted and the daily gonadotropin injections would still be required.

## 2. Follicular stimulation

The introduction of the GnRH antagonist protocol, which was characterized by rapid suppression of luteinizing hormone (LH) with fewer injections than previous protocols and reduced risk of ovarian hyperstimulation syndrome (OHSS) [5], was an advancement in the IVF armamentarium. This protocol serves as an important milestone in ad-

vanced reproductive treatments, because it enabled the IVF cycle to be decreased from four to five weeks to approximately two weeks in duration, with fewer injections [6]. Never the less, a significant number of injections in IVF cycles remain. It is clear, that the IVF protocols we currently use were developed in the late 1980s and modified with the introduction of the GnRH antagonists in the early 2000s.

About 15 years ago, utilizing recombinant DNA technologies, long-acting follicular stimulation hormone (LA-FSH) was developed for use in IVF. In this molecule the FSH  $\beta$ -subunit is extended by a carboxy-terminal peptide (CTP) of the human chorionic gonadotropin (hCG)  $\beta$ -subunit prolonging the half-life and providing it with 7 days of action [7]. LA-FSH has the ability to stimulate folliculogenesis in a patient for seven days with a single injection [7], with comparable outcomes to daily injections in assisted reproduction [8–10]. Fifteen years ago, severe OHSS affected up to 7% of IVF cases [11]. When the first commercially available LA-FSH was brought to market, its indication was the good responder patient. Clinicians were hesitant to use it in their patients, fearing an inability to decrease levels of FSH stimulation for 7 days and the resultant increased risks of OHSS [12]. This occurred prior to the widespread adoption of GnRH-agonist triggering and freeze all embryos for the prevention of OHSS [13,14]. At the time that the LA-FSH was first introduced to market, IVF practitioners claimed that it should be marketed for poor responder patients who would have low risks of OHSS



however, an appropriate dose and this indication was never introduced. Consequently, few prescriptions of LA-FSH were written. However, the concept of a single injection for FSH stimulation which could be given in the IVF clinic by the nurse at the time of initial cycle day 2 or 3 ultrasound, is intriguing, decreasing the need for patient self-injections. In countries where LA-FSH is still marketed its adoption has remained low, in spite of ideal protocols (GnRH-Antagonist) for its use, now being in place.

### 3. Prevention of a spontaneous LH surge

In addition to follicular stimulation, prevention of a spontaneous LH surge is required in IVF cycles [4,15]. More recently, oral progestins were employed to prevent the spontaneous LH surge, the approach of progesterone primed ovarian stimulation (PPOS). While the ideal protocol using oral progestins has yet to be determined, with questions related to; should they be started based on the lead follicle diameter or with the first day of gonadotropin stimulation, and the ideal dose to be used to prevent the LH surge remaining [16,17]. However, the use of provera 10 mg orally daily from the first day of FSH stimulation until the day of hCG triggering clearly is efficient at preventing premature ovulation [16,17].

A randomized controlled trial (RCT) by Giles *et al.* [18] compared the prevention of premature ovulation using either medroxyprogesterone acetate (MPA) 10 mg/day starting with stimulation as compared to the conventional GnRH antagonist IVF protocol. In both study groups, ovulation was induced using 0.2 mg subcutaneous triptorelin. There were no differences in the number of metaphase II oocytes retrieved, gonadotropin doses used, and ART success rates in the recipients. There were no cases of premature progesterone elevations or OHSS in either group [18]. In another RCT [19], which compared pregnancy outcomes after PPOS using 4 versus 10 mg of MPA per day in women with normal ovary reserve started simultaneously from cycle day 3, results were comparable in terms of the number of oocytes retrieved and pregnancy outcome after FET. The administration of 4 mg of MPA per day was sufficient to prevent an untimely LH rise in women undergoing IVF/Intracytoplasmic sperm injection (ICSI) treatment [19]. An alternative to the use of medroxyprogesterone acetate in PPOS is dydrogesterone (DYG) 20 mg/day started simultaneously from cycle day 3, which was proven to be appropriate progestin for PPOS in an RCT that included 516 patients younger than 36 years of age and with normal ovarian reserve, doing their first IVF/ICSI treatment [20]. Results were comparable in terms of the number of oocytes retrieved, viable embryo rate per oocyte retrieved and no patients experienced a premature LH surge [20]. Moreover, a recent meta-analysis that included 3565 cycles, revealed that PPOS is a safe option as a protocol for infertile patients [21]. There were no differences in clinical pregnancy rates and live birth rates, and the rate of OHSS was lower in the

PPOS protocol [21]. PPOS is a viable protocol to prevent a premature LH surge in IVF cycles [22].

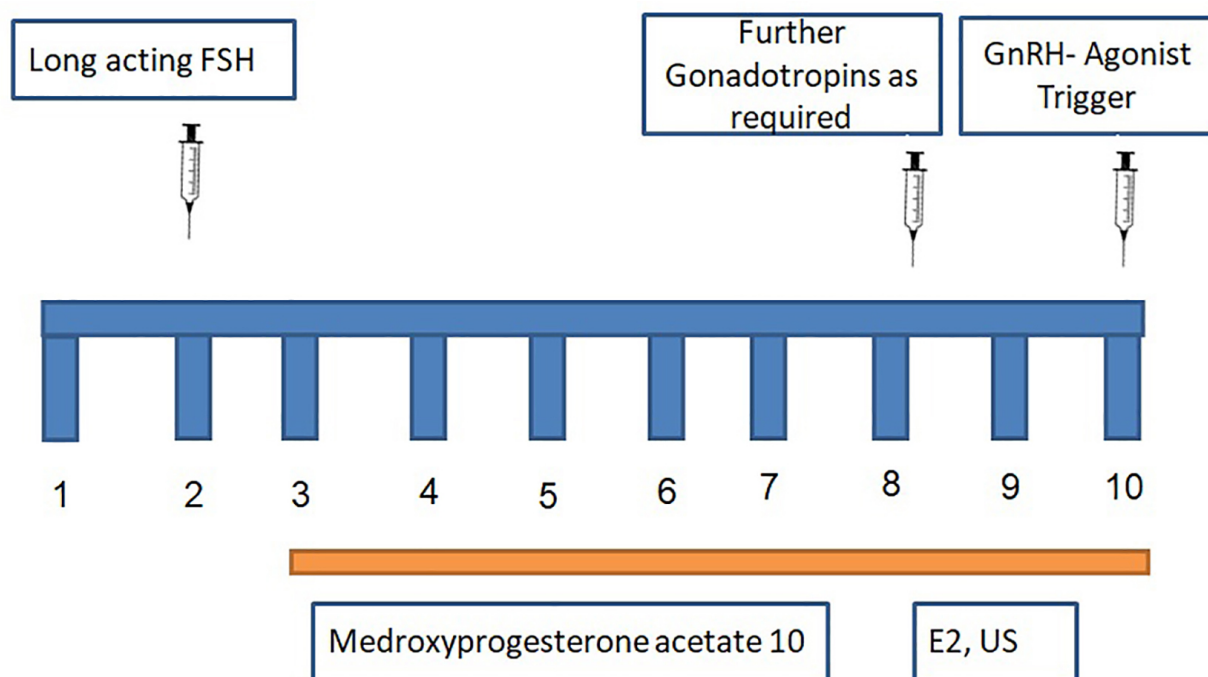
The drawback with PPOS is that the endometrium is luteinized and out of phase, preventing a fresh embryo transfer. However, fresh embryos transfers are becoming less common. There are many indications for freeze all cycles in current IVF practice. These include preimplantation genetic testing for aneuploidy (PGT-A) [23,24] and many studies that suggest better pregnancy outcomes and lower perinatal and neonatal complication rates in women who underwent frozen cycles [25–27]. Although, the validity of some of these indications can be debated, an increasing proportion of IVF cycles are freeze all [28].

One could substitute the intra-nasal GnRH agonist for the MPA to prevent ovulation and minimize injections. However, this would be as part of a long or microdose flair protocol and as such the GnRH agonist trigger could not be used and the risk of OHSS would increase.

One study found that the average number of gonadotropins injections in the GnRH antagonist protocol before trigger was  $23 \pm 8.5$  including  $5.7 \pm 2.3$  injections of the GnRH antagonist [29]. A similar protocol to the one we suggest adoption of, was previously studied in 45 patients and was shown to require on average 3.6 injections (range 2–9) [30]. A study by Requena *et al.* [31] comparing the experiences of ovum donors stimulated with LA-FSH who had previously stimulated with daily FSH, found that they were more satisfied with the LA-FSH [31] than with the previous daily gonadotropin stimulation. This finding was likely due to the decrease in injections. Although, the need for daily subcutaneous injections in infertility treatment does not tend to impair treatment adherence, it leads to patient anxiety regarding the possibility of making medication errors [3]. To improve compliance, we should try to make protocols as simple as possible.

In a Cochrane database review [32], comparing the effectiveness of LA-FSH versus daily FSH in terms of pregnancy and safety outcomes in women undergoing IVF or ICSI treatments, which included six randomized controlled trials in 3753 women, there was no evidence of difference in the effect on live birth rates in women receiving a medium dose (150 to 180  $\mu$ g) of long-acting FSH compared to daily FSH. The meta-analyses of outcomes of clinical pregnancy and ongoing pregnancy did not show evidence of a difference between LA and daily FSH at any dosage. Similarly, there was no evidence of a difference in adverse events for: multiple pregnancy rates, miscarriage rates, ectopic pregnancy rates and congenital malformations (major or minor) between LA-FSH and daily FSH [32].

We suggest the use of a single injection of LA-FSH based on body weight, ovarian reserve parameters and previous stimulation experience for IVF stimulation. Medroxyprogesterone acetate 4 or 10 mg orally daily should be initiated from the day after LA-FSH injection or a different progestin, if evidence based, if preferred (Fig. 1). As



**Fig. 1. A better IVF protocol.**

indicated, follicle development will be monitored per the clinic protocol. If needed seven days after the injection of LA-FSH a few days of gonadotropin stimulation or another single shot of LA-FSH could be administered based on follicular measurements. The patients could then be triggered for oocyte collection with a GnRH-agonist. The embryos would be frozen to transfer in a subsequent cycle. This would be an ideal protocol mainly for normal or high responders, when freeze all could be anticipated by the clinician. Although, this protocol could be used in caution with poor responders, it should be noted that the long acting FSH was not indicated in this group and some poor responders are not ideal candidates to freeze all embryos.

#### 4. Conclusions

LA-FSH was initially brought to market by one pharmaceutical company and a second was in development of a similar product but stopped the development. This occurred because of a lack of enthusiasm in the market place for LA-FSH. Much has changed in IVF since the first introduction of LA-FSH. Many of the factors which caused this lack of enthusiasm are no longer issues. We can prevent OHSS in most cases with GnRH agonist triggering of oocyte maturation and freeze all cycle have become common place with many indications. LA-FSH protocols with the use of progestins to prevent ovulation could be an alternative way to treat IVF patients without any compromise of the effectiveness of the treatments or the safety of the patients. Simplifying treatment protocols would help reduce physical and emotional demands for patients. The first injection of LA-FSH could be delivered by the nurse in the

clinic, aiding patients with difficulties self-performing injections. We have had for a long time the technology for a more patient friendly experience in IVF; we finally have the techniques and evidence to adopt this product. We call on the relevant drug companies to re-introduce LA-FSH to market in North America, unlike when initially proposed the market should now be ready for the role out.

#### Author contributions

EKP—conceptualization and research for the study, drafting the article and revising it. MHD—conceptualization and design of the study, revising it critically for important intellectual content, final approval of the version to be submitted. MHD acted as the senior author. All authors read and approved the final manuscript.

#### Ethics approval and consent to participate

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#### Conflict of interest

The authors declare no conflict of interest. MHD is serving as Editor-in-Chief and one of the Guest Editors of this journal. We declare that MHD had no involvement in the peer review of this article and has no access to infor-

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